DDX6 Orchestrates Mammalian Progenitor Function through the mRNA Degradation and Translation Pathways.

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Public Summary:
It is currently unclear how the skin maintains its remarkable regenerative capacity due to normal turnover or recovery from injury. We show here that the RNA helicase, DDX6 is required to promote the translation of known proteins involved in promoting epidermal self-renewal and proliferation. This translation of these critical regulators allows for the basal layer of the epidermis to sustain itself over long periods of time. Furthermore, DDX6 interacts with mRNA decay proteins to target and degrade mRNAs that would normally promote premature epidermal differentiation including transcription factor KLF4. By keeping the levels of KLF4 low, DDX6 can prevent premature differentiation. Thus, DDX6 acts in two different ways by interacting with both the mRNA degradation and translation pathways.

Scientific Abstract:
In adult tissues, stem and progenitor cells must balance proliferation and differentiation to maintain homeostasis. How this is done is unclear. Here, we show that the DEAD box RNA helicase, DDX6 is necessary for maintaining adult progenitor cell function. DDX6 loss results in premature differentiation and decreased proliferation of epidermal progenitor cells. To maintain self-renewal, DDX6 associates with YBX1 to bind the stem loops found in the 3' UTRs of regulators of proliferation/self-renewal (CDK1, EZH2) and recruit them to EIF4E to facilitate their translation. To prevent premature differentiation of progenitor cells, DDX6 regulates the 5' UTR of differentiation inducing transcription factor, KLF4 and degrades its transcripts through association with mRNA degradation proteins. Our results demonstrate that progenitor function is maintained by DDX6 complexes through two distinct pathways that include the degradation of differentiation-inducing transcripts and by promoting the translation of self-renewal and proliferation mRNAs.